

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year)

12 November 2001 (12.11.01)

International application No.

PCT/GB00/02014

Applicant's or agent's file reference

JHC/P40513WO

International filing date (day/month/year)

05 June 2000 (05.06.00)

Priority date (day/month/year)

03 June 1999 (03.06.99)

Applicant

FRANKS, Christopher, Ralph et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

18 December 2000 (18.12.00)



in a notice effecting later election filed with the International Bureau on:

2. The election



was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

BEST AVAILABLE COPY

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Marie-Christine GUILLEMOT

Telephone No.: (41-22) 338.83.38

AAAAE214

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year)
25 January 2001 (25.01.01)

International application No.
PCT/GB00/02014

Applicant's or agent's file reference
JHC/P40513WO

International filing date (day/month/year)
05 June 2000 (05.06.00)

Priority date (day/month/year)
03 June 1999 (03.06.99)

Applicant

FRANKS, Christopher, Ralph et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
18 December 2000 (18.12.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

BEST AVAILABLE COPY

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

GB0002014

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HARRISON GODDARD FOOTE
Belgrave Hall
Belgrave Street
Leeds LS2 8DD
ROYAUME-UNI

Date of mailing (day/month/year)

27 November 2001 (27.11.01)

Applicant's or agent's file reference

JHC/P40513WO

IMPORTANT NOTIFICATION

International application No.

PCT/GB00/02014

International filing date (day/month/year)

05 June 2000 (05.06.00)

1. The following indications appeared on record concerning:

☐ the applicant

☐ the inventor

☒ the agent

☐ the common representative

Name and Address

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
United Kingdom

State of Nationality

State of Residence

Telephone No.

44 113 290 1400

Facsimile No.

44 113 245 6848

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person

☐ the name

☒ the address

☐ the nationality

☐ the residence

Name and Address

HARRISON GODDARD FOOTE
Belgrave Hall
Belgrave Street
Leeds LS2 8DD
United Kingdom

State of Nationality

State of Residence

Telephone No.

+44 113 233 0100

Facsimile No.

+44 113 233 0101

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office

☐ the International Searching Authority

☒ the International Preliminary Examining Authority

☐ the designated Offices concerned

☒ the elected Offices concerned

☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Victoria CORTIELLO

Telephone No.: (41-22) 338.83.38

004488022

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HARRISON GODDARD FOOTE
Belgrave Hall
Belgrave Street
Leeds LS2 8DD
ROYAUME-UNIRECEIVED
JUL 18 2002
TECH CENTER 1600/2900

Date of mailing (day/month/year)

11 December 2001 (11.12.01)

Applicant's or agent's file reference

JHC/P40513WO

International application No.

PCT/GB00/02014

IMPORTANT NOTIFICATION

International filing date (day/month/year)

05 June 2000 (05.06.00)

1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

BIOINNOVATION LIMITED
79 The Broadway
Stoneleigh
Epsom
Surrey KT17 2HP
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:



the person



the name



the address



the nationality



the residence

Name and Address

BIOINNOVATION LIMITED
17 Hanover Square
London W1R 9AJ
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:



the receiving Office



the International Searching Authority



the International Preliminary Examining Authority



the designated Offices concerned



the elected Offices concerned



other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Buttay

Telephone No.: (41-22) 338.83.38

004525734

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

17.OCT.2001*064847

Date of mailing
(day/month/year)

15.10.2001

Applicant's or agent's file reference
JHC/P40513WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02014

International filing date (day/month/year)
05/06/2000

Priority date (day/month/year)
03/06/1999

Applicant

BIOINNOVATION LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.


4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hingel, W

Tel. +49 89 2399-8717




PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JHC/P40513WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/02014	International filing date (day/month/year) 05/06/2000	Priority date (day/month/year) 03/06/1999	
International Patent Classification (IPC) or national classification and IPC A61K48/00			
Applicant BIOINNOVATION LIMITED et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input checked="" type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 18/12/2000		Date of completion of this report 15.10.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Nichogiannopoulou, A Telephone No. +49 89 2399 8054	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02014

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)
- Description, pages:**

1-34 as originally filed

Claims, No.:

1-48 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02014

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

- ☐ copy of the earlier application whose priority has been claimed.
☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-48, all partially.

because:

- ☒ the said international application, or the said claims Nos. 46 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☒ the claims, or said claims Nos. 1-48, all partially are so inadequately supported by the description that no

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02014

meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-48, all partially.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-48
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-48
Industrial applicability (IA)	Yes:	Claims 1-45, 47, 48
	No:	Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02014

Re Item II

Priority

1. The following document was published prior to the international filing date but later than the priority date claimed (P-document):

P1: WO 99 26660 A (BIOINNOVATION LIMITED; DELLA BITTA RUGGERO (GB); FRANKS CHRISTOPHE) 3 June 1999 (1999-06-03)

2. The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (03.06.1999). If it later turns out that this assumption is incorrect, P1 will become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(2) and (3) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No meaningful examination could be performed for claims 1-48, all partially, for the following reasons:
 - 1.1. Rule 66. 1.(e) (PCT):
No complete international search report has been established for said claims (see Form PCT/ISA/210 issued on 08/02/2001). Accordingly, said claims need not be the subject of international preliminary examination.

- 1.2. Article 6 PCT:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02014

Claims 1-48 relate to an extremely large number of possible combinations of a three-component conjugate. The broad wording of a claim does not justify the examination to be carried out beyond the extent to which the claimed subject-matter is sufficiently disclosed in the application (Article 5 PCT) and supported by the description (Article 6 PCT). In the present case the claims so lack support and the application so lacks disclosure that a meaningful examination over the whole of the claimed scope is impossible. Since none of the claimed compounds is exemplified in the description, examination was limited to the general idea underlying the application.

2. Claim 46 -as far as it concerns *in vivo* methods- relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: WO 96 36362 A (PRIZM PHARMA INC) 21 November 1996 (1996-11-21)
- D2: CRISTIANO R J ET AL: 'Epidermal growth factor mediated DNA delivery into lung cancer cells via the epidermal growth factor receptor.' CANCER GENE THERAPY, vol. 3, no. 1, 1996, pages 4-10, XP000577163
- D3: SOSNOWSKI B A ET AL: 'Targeting DNA to cells with basic fibroblast growth factor (FGF2).' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 52, 1996, pages 33647-33653, XP002067516 ISSN: 0021-9258
- D4: WO 95 28494 A (TARGETED GENETICS) 26 October 1995 (1995-10-26)
- D5: WO 92 20364 A (SERAGEN INC) 26 November 1992 (1992-11-26) cited in the application
- D6: KONIGSBERG PJ ET AL: 'The development of IL-2 conjugated liposomes

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02014

for therapeutic purposes' BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1370,
13 March 1998 (1998-03-13), pages 243-251, XP002110538 ISSN: 0005-
2736

- D7: BUKOWSKI R M: 'Natural history and therapy of metastatic renal cell carcinoma. The role of interleukin-2' CANCER, US, AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, vol. 80, no. 7, 1 October 1997 (1997-10-01), pages 1198-1220, XP002097613 ISSN: 0008-543X
- D8: 'CHIRON PROLEUKIN (ALDESLEUKIN) FOR INJECTION PRESCRIBING INFORMATION (UNITED STATES)' CHIRON, US, ANN RUEL STUDIO GRAPHICS, SCARBOROUGH, ME, January 1998 (1998-01), XP002110539 ISSN: 1081-8685

2. Novelty and Inventive step (Article 33(2) and (3) PCT)

- 2.1. The present application discloses a three-component conjugate for gene therapy comprising: i) a proliferatively active moiety such as a cytokine or a growth factor, ii) a nucleic acid material and iii) a protective material associated therewith. The proliferation inducing moiety is used as a vector to deliver the protected nucleic acids into target cells. A conjugate of the proliferation inducing protein with a protected (e.g. encapsulated) nucleic acid is claimed although not disclosed.

Three-component conjugates for gene therapy are already known from the prior art.

D1 discloses therapeutic conjugates comprising i) a receptor binding moiety such as cytokine or growth factor, ii) a nucleic acid molecule encoding a cytocide and iii) a nucleic acid binding domain such as poly-L-lysine. **D2** also discloses a targeted DNA delivery system for the treatment of lung cancer, comprising epidermal growth factor coupled to polylysine complexed with DNA. Beta-gal is exemplified but the use of therapeutic genes is contemplated. The combined teachings of **D1** and **D2** are detrimental to the novelty and inventive step of claims 1-48, in as far as examination of these claims was possible (see item III).

- 2.2. For the sake of completion it is furthermore noted that **D3** discloses the targeting of DNA into cells by conjugating to FGF conjugated to polylysine. **D4** discloses gene delivery fusion proteins comprising i) a nucleic acid binding domain that

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02014

binds the targeted nucleic acid and ii) a gene delivery domain that mediates or augments gene transfer. IL-2 is exemplified as the gene delivery domain. **D5** is a general disclosure of targeted gene therapy using interleukin receptors. **D6** discloses the targeting of methotrexate to activated T-cells by coupling to IL-2. **D7** teaches the role of IL-2 and IFN-alpha in tumour therapy. **D8** teaches the general pharmacology on Aldesleukin. Aldesleukin has been shown to possess the biological activities of human native interleukin-2.

The combined teachings of **D1-D8** are detrimental to the novelty and inventive step of claims 1-48, to the extent that examination of these claims was possible (see item III).

3. Industrial applicability (Article 33(4) PCT)

The subject-matter of the claims for which an opinion has been established (see item III) appears to be industrially applicable under the terms of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(ii) PCT, documents **D1-D4** and **D6-D8** are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/74724 A3

- (51) International Patent Classification⁷: C12N 15/87, (74) Agent: HARRISON GODDARD FOOTE; Tower
C07K 14/52, A61K 48/00, 47/48, 38/00 House, Merrion Way, Leeds LS2 8PA (GB).
- (21) International Application Number: PCT/GB00/02014 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
(22) International Filing Date: 5 June 2000 (05.06.2000) AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
(25) Filing Language: English DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
(26) Publication Language: English ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (30) Priority Data:
9912807.6 3 June 1999 (03.06.1999) GB (84) Designated States (*regional*): ARIPO patent (GH, GM,
60/137,592 3 June 1999 (03.06.1999) US KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): BIOIN-
NOVATION LIMITED [GB/GB]; 79 The Broadway,
Stoneleigh, Epsom, Surrey KT17 2HP (GB).
- (72) Inventors; and
(75) Inventors/Applicants (*for US only*): FRANKS, Christo-
pher, Ralph [GB/GB]; Church House, Wantage Road, Ed-
dington, Hungerford RG17 2HP (GB). DELLA BITTA,
Ruggiero [IT/IT]; Corso Porta Romana 74, I-20122 Mi-
lan (IT). MAITLAND, Norman, James [GB/GB]; Can-
cer Research Unit, Biology Department, The University of
York, York YO1 5YW (GB). KNIGHT, David, Jonathan
[GB/GB]; Cancer Research Unit, Biology Department, The
University of York, York YO1 5YW (GB).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
12 July 2001
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CONJUGATES COMPRISING CYTOKINES AND NUCLEIC ACIDS FOR TREATING PROLIFERATING CELLS

(57) Abstract: A product comprising a proliferatively active moiety linked to genetic or nucleic acid material which is associated with protective material. The proliferatively active moiety is typically a cytokine or growth factor. The protective material may form a micelle, especially a liposome, which may encapsulate the nucleic acid material or be positively charged and hold the nucleic acid on its surface (a so-called lipoplex). One class of protective materials, therefore, comprises complexing materials and includes not only cationic liposomes but also other cationic materials, especially polymers. As suitable polymers there may be mentioned polylysine (especially poly-D-lysine), polylysine derivatives (e.g. phospholipid derivatives of, in particular, poly-L-lysine) and polyethyleneimine (PEI). Other suitable complexing agents are dendrimers, especially polyamidoamine dendrimers (which are cationic). The genetic or nucleic acid material may be a cytotoxic gene, a defect correction gene or an immunogene. Suitable cyto-
toxic genes are for expressing an enzyme to convert a prodrug into a toxic drug.

WO 00/74724 A3

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JHC/P40513WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 02014	International filing date (day/month/year) 05/06/2000	(Earliest) Priority Date (day/month/year) 03/06/1999
Applicant BIOINNOVATION LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

CONJUGATES COMPRISING CYTOKINES AND NUCLEIC ACIDS FOR TREATING PROLIFERATING CELLS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/87 C07K14/52 A61K48/00 A61K47/48 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, MEDLINE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 36362 A (PRIZM PHARMA INC) 21 November 1996 (1996-11-21) page 54, line 7 -page 55, line 26; claims 1,5,16,19,28,30,31	1-48
X	CRISTIANO RICHARD J ET AL: "Epidermal growth factor mediated DNA delivery into lung cancer cells via the epidermal growth factor receptor." CANCER GENE THERAPY, vol. 3, no. 1, 1996, pages 4-10, XP000577163 ISSN: 0929-1903 the whole document	1-48

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 November 2000

Date of mailing of the international search report

08.02.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Nichogiannopoulou, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	' SOSNOWSKI BARBARA A ET AL: "Targeting DNA to cells with basic fibroblast growth factor (FGF2)." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 52, 1996, pages 33647-33653, XP002067516 ISSN: 0021-9258 the whole document	1-48
Y	WO 95 28494 A (TARGETED GENETICS CORP; OVERELL ROBERT W (US); WEISSER KAREN E (US) 26 October 1995 (1995-10-26) page 42, line 22 -page 43, line 9; examples 2,7,10-12	1-48
Y	WO 92 20364 A (SERAGEN INC) 26 November 1992 (1992-11-26) cited in the application the whole document	1-48
Y	' KONIGSBERG PJ ET AL: "The development of IL-2 conjugated liposomes for therapeutic purposes" BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1370, 13 March 1998 (1998-03-13), pages 243-251, XP002110538 ISSN: 0005-2736 the whole document	1-48
Y	' BUKOWSKI R M: "Natural history and therapy of metastatic renal cell carcinoma. The role of interleukin-2" CANCER,US,AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, vol. 80, no. 7, 1 October 1997 (1997-10-01), pages 1198-1220, XP002097613 ISSN: 0008-543X the whole document	1-48
Y	' "CHIRON PROLEUKIN (ALDESLEUKIN) FOR INJECTION PRESCRIBING INFORMATION (UNITED STATES)" CHIRON,US,ANNRUEL STUDIO GRAPHICS, SCARBOROUGH, ME, January 1998 (1998-01), XP002110539 ISSN: 1081-8685 the whole document	1-48
P,X, L	WO 99 26660 A (BIOINNOVATION LIMITED; DELLA BITTA RUGGERO (GB); FRANKS CHRISTOPHE) 3 June 1999 (1999-06-03) L: priority the whole document	29,30

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 46 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: **1-48 all partially**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 - 48 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-48 all partially

Present claims 1-48 relate to an extremely large number of possible combinations of a three-component conjugate. The broad wording of a claim does not justify the search to be carried out beyond the extent to which the claimed subject-matter is sufficiently disclosed in the application (Article 5 PCT) and supported by the description (Article 6 PCT). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Since none of the claimed compounds is exemplified in the description, the search was limited to the general idea underlying the application (see Guidelines B III 3.7).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-48 all partially

A product comprising IL-2 linked to a cytotoxic gene associated with a cationic polymer. The use of such a product for the manufacture of a medicament, pharmaceutical formulations and methods of treatment comprising such products.

2-288. Claims: 1-48 all partially

A product comprising a proliferatively active moiety linked to a nucleic acid material associated with protective material, wherein the proliferatively active moiety is selected from the group consisting of: IL-2, IL-6, TNF, M-CSF, IFN-alpha, IFN-beta, IFN-gamma, FGF, IGF-1, TGF-beta, GM-CSF, SCF, G-CSF, Epo, Multi-CSF, E-CSF, PDGF and TGF-beta2, the nucleic acid material is selected from the group consisting of a cytotoxic gene, a defect correction gene, an immunogene, thymidine kinase, cytosine deaminase, cytochrome P-450, bacterial nitroreductase and an anti-sense nucleotide sequence and the protective material is selected from the group consisting of cationic liposomes and cationic polymers. The use of such a product for the manufacture of a medicament, pharmaceutical formulations and methods of treatment comprising such products.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02014

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9636362	A	21-11-1996	AU 3374795 A	22-03-1996
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			EP 0584251 A	02-03-1994
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